using said multi-photon excitation, photoactivating said at least one agent over said range of depths within said tissue, thereby producing at least one photo-activated agent substantially only at the focal zone.

Claim ~~107~~ 113 (Amended). A method for the treatment of a particular volume of plant or animal tissue, the tissue including at least one photoactive agent in the particular volume, the method comprising:

illuminating said particular volume of tissue to cause multi-photon excitation of said at least one photo-active agent,

wherein said at least one photo-active agent at a site of said multi-photon excitation is firstly excited to a transient virtual state and secondly excited to a quantum mechanically allowed excited state and wherein the at least one excited photo-active agent becomes photo-activated in the particular volume.

REMARKS

Applicants have the following response to the Office Action of April 24, 2001

I. ELECTION / RESTRICTIONS

Applicants affirm the election to prosecute Claims 1-116, 132-135, and 139-141 in the above-identified application. Applicants are making this election without prejudice to pursuing the non-elected claims in a divisional application.

II. DOUBLE PATENTING

The Examiner also rejects Claims 1-33 and 73-106 under judicially created doctrine of obviousness-type double patenting in view of claims 1-68 of U.S. Patent No. 5,829,448. The Examiner further rejects Claims 34-106 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 5,998,597.

Two terminal disclaimer are being filed herewith. Accordingly, it is respectfully submitted that this rejection has now been overcome.

If any fee should be due for these terminal disclaimers, please charge our deposit account 50/1039.

II. CLAIM REJECTIONS - 35 USC §112

The Examiner also has rejected Claims 25, 64, 101 and 107 under 35 USC §112 for being indefinite.

A. Claims 25, 64, and 101

The Examiner states that Claims 25, 64, and 101 are allegedly indefinite because it is unclear as to the definition of a "photophysical" process. This rejection is respectfully traversed.

Applicants submit that not only is this a term that is well known in the art but also that it is clearly defined in the specification. It is well established law that the specification can define a term in the claims.

More specifically, in the specification of the present application, the terms "photochemical" and "photophysical" processes are used consistently at numerous locations. For example,

"... by varying the instantaneous irradiance delivered to the agent (at a given specific photon energy), the energy of the excited state can be varied according to the relationship, E = n hv, where n is the number of photons absorbed. As this energy is increased, for example by increasing the pulse energy of a laser excitation source, the *therapeutic outcome* of the interaction of light with an agent *can be shifted from a substantially photochemical process to a substantially photophysical process*, as shown diagrammatically in FIGURE 4. At low relative pulse energies, for example less than 10 nJ delivered in a 200 fs pulse, *photochemical excitation* (40) via two- or three-photon processes will typically predominate. However, at high relative pulse energies, for example greater than 100 μJ delivered in a 200 fs pulse, *photophysical excitation* (42) via a four- or more photon process will typically predominate. At intermediate relative pulse energies a *combination outcome* (44) is possible (*part photochemical, part photophysical* in nature, such as thermal denaturation or highly localized coagulation). Thus, use of the present multi-photon methods allows therapeutic processes to be shifted between regimes ranging from photodynamic to ablative." (page 22, lines 9-23, emphasis added)

In this passage, a photochemical process is one in which photochemistry is stimulated[1], while a photophysical process is one in which a physical change is stimulated. The meaning of such a photophysical process is further clarified in the specification:

"Note that sources capable of emitting relatively low energy pulses (such as the mode-locked titanium:sapphire laser, with typical pulse energies in the range of 1-10 nJ) are optimally suited to *photochemical activation of agents* (*such as PDT*) using two- or more photons under focused illumination conditions, while *sources capable of emitting relatively high energy pulses* (such as the regeneratively amplified titanium:sapphire laser, with typical pulse energies in the range of 1-10 μJ) are *optimally suited* to *photophysical activation* of

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[1] The Photonics Dictionary, year 2000 edition, by Laurin Publishing (the cited portions being attached to the IDS enclosed herewith), defines "photochemistry" as "[t]he study of chemical reactions stimulated by the properties of light". Thus a photochemical process is a process in which a chemical reaction is stimulated by application of light. An example of a photochemical process is the stimulation of a PDT agent into a therapeutically active state upon application of low intensity laser light.

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agents (*such as ablation*) using two- or more photons under focused illumination conditions. (page 35, lines 1-7, emphasis added)

Thus, an example of a claimed substantially photophysical process is ablation.[2] Another example of a substantially photophysical process is tissue denaturation, as described by the following passage in the specification:

> "*Tissue denaturation* is a localized, *combination photochemical and photophysical process* resulting from rapid heating of endogenous or exogenous agents. Such heating results from conversion of incident optical energy into thermal energy upon absorption of such optical energy by one or more endogenous or exogenous agents (such as for example blood). *Denaturation can result in change of volume* of such agents or of surrounding tissues (such as shrinkage or expansion of corneal stem cells), *change in physical properties* (such as hardness of dental enamels), *or initiation of polymerization* (such as coagulation of blood). The multi-photon photo-activation methods taught in the present invention, when used to activate responsive agents, allow improved control over the site of such denaturation as a consequence of the decreased loss of activating energy to surrounding tissue when such response is stimulated using ultrashort pulsed excitation. Specifically, the present invention enables improved localization in the photo-activation of responsive agents with significantly reduced potential for collateral tissue damage compared with that possible using conventional methods." (page 36, line 23 - page 37, line 12, emphasis added)

Such denaturation is described in this passage as resulting from a combination of photochemical and photophysical processes, and is described schematically by Figure 4 in the present application. In general, such denaturation will primarily result from photophysical stimulation of the treated material (i.e., heating), but may also include a photochemical component, and is thus correctly described here as the result of a combination of photochemical and photophysical processes.

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[2] The Photonics Dictionary, *ibid*, defines "laser ablation" as "1. The use of a laser to remove body tissue as if by surgery, but actually by vaporization; 2. The use of a laser to remove material by vaporization..." This reference book defines "ablation" as "see laser ablation".

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Thus, as described in the specification of the present application, a "photophysical" process comprises non-photochemical, photo-initiated changes to a material, such as denaturation or ablation. Hence, it is respectfully submitted that the term "photophysical process" is clearly defined in the specification.

Further insight into this nomenclature is provided upon review of Niemz's chapter on laser interaction mechanisms with biological tissue.[3] Niemz divides the major types of laser interaction into several categories (see page 45), according to certain fundamental properties of the respective interaction mechanisms:

- Photochemical Interaction (section 3.1, page 47 et seq.)
- Thermal Interaction (section 3.2, page 58 et seq.)
- Photoablation (section 3.3, page 86 et seq.)
- Plasma-Induced Ablation (section 3.4, page 101 et seq.)
- Photodisruption (section 3.5, page 124 et seq.)

Review of the respective sections on each of these topics illustrates that "photochemical interactions" are the result of light-induced chemical reactions. In contrast, the other listed types of interaction are the direct result of photophysical effects. Specifically, thermal interactions (such as coagulation, vaporization, carbonization, and melting, see pages 58-59) result from local increase in temperature upon absorption of applied light energy (i.e., a photophysical process) (pages 58 et seq.). Photoablation (or ablative photodecomposition, see page 86) results from photo-induced disruption of bonds within a molecule or between molecules (a photophysical process) (pages 86 et seq.).

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[3] See, M.H. Niemz, Laser-Tissue Interactions, Fundamentals and Applications, Springer-Verlag, Berlin, 1996, pp. 45-147 (attached to enclosed IDS).

Plasma-induced ablation (or plasma-mediated ablation, see page 103) results from generation of photo-induced plasma (a photophysical process) (pages 103 et seq.). Photodisruption results from photo-induced shock waves produced within or proximal to a material (a photophysical process) (pages 124 et seq.).

Thus, the terms "photochemical" and "photophysical" are sufficiently clear to those skilled in the art in the field of the invention to understand and apply the teachings of the present application, and that the usage of such terms in the specification and in the appended claims thereto is consistent with such use in the field. Hence, the use of this term in Claims 25, 64, and 101 does not render indefinite the claims. Accordingly, it is requested that this objection be withdrawn.

B. Claim 107

The Examiner also has a specific objection to Claim 107 on the basis of alleged indefiniteness regarding the subject of the excitation process. Applicants have amended this claim to clarify the predicate relationship of the photo-active agent.[4] Applicants believe that such amendment resolves any alleged indefiniteness.

Accordingly, it is respectfully submitted that the claims are not indefinite, and it is requested that the §112 rejections be withdrawn.

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[4] The amendment to this claim, and similar amendments to the other claims, is made to correct an informality in the claim. It is not intended as a Festo narrowing of the claim.

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III. CLAIM REJECTIONS - 35 USC §102

The Examiner has rejected Claims 1, 2, 5, 6, 7, 8, 16-19, 22, 27, 28, 30, 31, 33-39, 42, 45-48, 56-58, 61, 65-67, 69, 70, 132, and 133 under 35 USC §102 as being anticipated by Kawai et al. In reference to these claims, the Examiner contends that Kawai et al. disclose a *method for treating tissue with light to promote a multi-photon photo-activation* of at least one photo-active agent in the tissue.

Kawai et al., however, teaches only a *sequential two-photon excitation* (TPE) method for PDT. Specifically col. 2 lines 61-66 and claims 1 and 12 describe a *sequential, two-step excitation* method wherein a first of two photons is absorbed to initially promote a sensitizer molecule from the ground state to a quantum mechanically allowed excited electronic state (i.e., S_0 to S_1); after partial relaxation to the lowest excited triplet state, the molecule is further excited to a more energetic triplet state (i.e., T_1 to T_n) upon absorption of a second of two photons. Both of the excitation steps used by Kawai et al. require quantum mechanically allowed electronic transitions, and hence the energy of each photon must be adequate to fully promote its respective allowed transition.

The sequential two-photon process of Kawai et al. is clearly illustrated and discussed in the parent filing for the present application (i.e., see ***32*** of Figure 1, USP 5,829,448). Such sequential TPE processes are completely different from the simultaneous multi-photon excitation processes described in both the parent application (i.e., 08/739,801) and by the present application. Specifically, the present application describes multi-photon processes that do not require that each transition match a quantum mechanically allowed transition, and which occur upon substantially simultaneous interaction of two or more photons with the treated material. Hence, while Kawai et al. is restricted to use of energies that are linearly absorbed by the molecule (i.e., <700 nm for the various porphyrin

examples provided), excitation using the MPE methods taught in the present application is not encumbered by such restrictions.

Solely for the sake of clarity, Applicants have amended independent Claims 1 and 34 to recite use of "substantially simultaneous multi-photon photoactivation". Kawai et al. clearly does not disclose or suggest such subject matter.[5]

Support for such amendment may be found throughout the specification of the present application, such as for example in the following passage:

> "A more *general definition of multi-photon excitation* than that given above requires only that the *two or more photons interact* with the one or more agents *in a substantially simultaneous manner*, for example any interaction occurring during a single ultrashort laser pulse having a duration of approximately 10 ps or less. Under such constraints, the interaction of light with the one or more agents must occur in the fast regime, substantially limiting (and localizing) the direct photo-activation effect to intra-molecular processes, such as electronic excitation or photoionization of the agent. No significant elapse of time nor substantial molecular reorganization nor motion will occur during such excitation, and on conventionally observable frames of reference any transitions thereby effected in the one or more agents will occur as an essentially single, concerted step. *This more general definition shall be used in subsequent descriptions of the properties of multi-photon excitation* and of the resultant multi-photon photo-activation of therapeutic agents." (col. 20 , lines 13-24, emphasis added)

And in the following passage:

> "Additionally, the excitation cross-sections for multi-photon processes generally decrease as the number of photons required for a given transition increases. For example, the three-photon cross-section for a particular transition in a given agent will generally be lower than the respective two-photon cross-section for the same transition. This is at least in part due to the reduced probability that all photons

[5] Applicants do not believe that this amendment is a narrowing of the scope of the claim but making it consistent with the teachings in the specification.

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necessary for a particular *multi-photon process* will interact with the agent in a *substantially simultaneous manner*." (col. 24 , lines 7-12, emphasis added)

Finally, in the following passage:

> "Excitation sources for multi-photon photo-activation:
> The cross-section for a particular *multi-photon excitation* process is typically many-fold smaller than that for an equivalent single-photon excitation process yielding the same activated state as the multi-photon process. This is due to the relatively low probability that *two or more photons will interact with an agent in a substantially simultaneous manner*." (col. 34 , lines 1-5, emphasis added)

Hence, it is respectfully submitted that the methods of independent Claims 1 and 34 are clearly distinct from the teachings in Kawai et al., and thus that these claims and all claims dependent thereon (i.e., Claims 1, 2, 5, 6, 7, 8, 16-19, 22, 27, 28, 30, 31, 33-39, 42, 45-48, 56-58, 61, 65-67, 69, 70, 132, and 133) are thereby patentable over this reference.

IV. ALLOWABLE SUBJECT MATTER

The Examiner has stated that Claims 107-116 and 135 would be allowable if rewritten or amended to overcome the rejection under 35 USC §112, second paragraph, set forth in the first Office action. As described *supra*, Applicants have amended Claim 107 so as to clarify the predicate relationship of the photo-active agent and that such amendment resolves any alleged indefiniteness of this independent claim and all claims dependent thereon.

Accordingly, it is requested that these claims be allowed.

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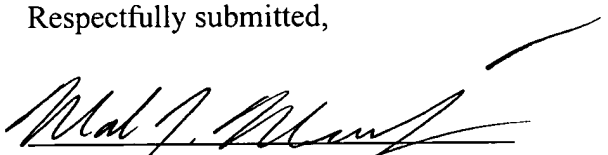
Conclusion

For the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable condition and are neither disclosed nor suggested by the cited reference and are patentable thereover. Accordingly, it is requested that the claims be passed to allowance.

If any fee should be due for this amendment, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,



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Marked-up copy of the claims as amended:

Claim 1 (Amended). A method for the treatment of a particular volume of plant or animal tissue, the method comprising the steps of:

(a) treating the plant or animal tissue with at least one photo-active agent, wherein the particular volume of the plant or animal tissue retains at least a portion of the at least one photo-active agent; and

(b) treating the particular volume of the plant or animal tissue with light to promote a substantially simultaneous multi-photon photoactivation [of at least one] of said at least one photo-active agent retained in the particular volume of the plant or animal tissue, wherein the at least one excited photo-active agent becomes photo-activated in the particular volume of the plant or animal tissue.

Claim 34 (Amended). A method for producing at least one photo-activated agent in a particular volume of a material, the method comprising treating the particular volume of the material with light to promote a substantially simultaneous multi-photon excitation of at least one photo-active agent contained in the particular volume of the material, wherein the at least one photo-active agent becomes a photo-activated agent in the particular volume of the material.

Claim 73 (Amended). A method for the medical treatment of a particular volume of tissue wherein the tissue includes at least one photo-active agent, the method comprising the steps of:

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directing light to specific regions of interest within the tissue, including regions substantially below a tissue surface, said light being selected to penetrate the tissue and to promote multi-photon excitation substantially only at a focal zone;

controlling the location of said focal zone over a range of depths within said tissue; and

using said multi-photon excitation, photoactivating [at least one of] said at least one agent over said range of depths within said tissue, thereby producing at least one photo-activated agent substantially only at the focal zone.

Claim 107 (Amended). A method for the treatment of a particular volume of plant or animal tissue, the tissue including at least one photoactive agent in the particular volume, the method comprising:

illuminating said particular volume of tissue to cause multi-photon excitation [of at least one] of said at least one photo-active agent,

wherein said at least one photo-active agent at a site of said [the] multi-photon excitation is firstly excited to a transient virtual state and secondly excited to a quantum mechanically allowed excited state and wherein the at least one excited photo-active agent becomes photo-activated in the particular volume.

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